VAST INCREASE IN SECOND PRIMARY LUNG CANCERS IN SWEDEN

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CONFLICT OF INTEREST

A.H. is the shareholder in Circio Holdings ASA. A.H. is an employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

ABSTRACT

Background: We describe the occurrence of second primary lung cancers (SPLCs) and their determinant in Sweden.

Methods: Nation-wide cancer registry from years 1961 to 2021 identified a total of 853 SPLCs.

Results: The incidence of SPLCs increased almost linearly from 1980 onwards, equally for women and men and approximately equally after the four main histological types. SPLC included adenocarcinoma 63.9%, squamous cell carcinoma (SCC) 19.4%, small cell carcinoma 9.6% and large cell carcinoma 9.1%. The female cumulative probability (CumP) of SPLC after first adenocarcinoma in 10 years reached 0.019, after SCC 0.015 and after small and large cell carcinoma

0.008. The respective CumP for men were 0.013, 0.012, 0.002 and 0.005. While adenocarcinoma was often followed by second adenocarcinoma, after first non-adenocarcinoma SPLCs presented in diverse histologies. Relative risk of SPLC compared to first lung cancer was overall 3.59, higher for women (4.16) than for men (2.99) and approximately equally high after adenocarcinoma and SCC. In patients diagnosed before age 55 years, the relative risk was 6.68 for all, but after female adenocarcinoma it was 9.95 compared to 6.77 for males. The highest relative risks, up to 20-fold, were found after early onset female adenocarcinoma diagnosed after defined T stages.

Conclusions: Although SPLCs are still rare their number is increasing rapidly and the relative risks compared to first lung cancer are substantial, qualifying selected groups of high-risk patients, such as early onset adenocarcinoma patients for early detection by CT screening when/if such tests become available.

KEY MESSAGE

- **What is already known on this topic** – Second primary lung cancers (SPLCs) increase as result of improving survival in first lung cancer.
- **What this study adds** - Novel data was provided on relative risk of SPLC, which was 4.16 for women and 2.99 for men, and as high as 10 after early-onset female adenocarcinoma.
- **How this study might affect research, practice or policy** – Follow-up schemes of lung cancer patients should consider risk-adjusted targeting.

Introduction

Survival has increased in lung cancer (LC) because of early diagnosis, improvements in treatment and changing histology towards the less fatal adenocarcinoma type (1, 2). Cure fraction or long-term survivors for LC were 8% for men and 10% for women in Europe by year 2000 (3). According to US data, cure rates depended on stage and histology, and by year 2015 the best cure fractions through 2020 were for adenocarcinoma stage I at 82%, decreasing to 6% for stage IV (4). A consequence of this positive development is an increasing likelihood that a patient will be diagnosed with an independent second primary LC (SPLC) (5, 6). For optimal treatment such independent primaries need to be distinguished from metastasis of the initial primary LC (IPLC) (6). To achieve this, commonly applied clinic-histological criteria (termed Martini-Melamed or MM criteria) define that between IPLC and SPLC: a) histological types need to be different or one tumor is in situ LC, or b) they may be the same histological type but diagnostic date of the second cancer needs to be at least 2 years later, or c) they may be the same histological type without time limit as long as the two tumors are located in different lobes or sides of lung with no involvement of lymphatics common to both and no evidence of extra pulmonary metastasis (see (5, 6)). For confirmation of the independent origins of IPLC and SPLC laboratory techniques have recently been developed and increasingly applied (5-7). These are used to establish clonal independence of SPLC by means of eg. immunohistochemistry, genome sequencing, comparative genomic hybridization or loss of heterozygosity analyses (5-7).

Many epidemiological studies on SPLC have been published despite of relatively low survival of LC patients (6, 8). Cancer registry-based studies do not use the above clinico-histological (MM) criteria for SPLC but may use their own or some international criteria for classifying second cancers as independent primaries (9-11). Many LC studies including data on SPLC covered in fact many types

of second cancers with main focus on etiology (rather than risk of SPLC), such as smoking (12-14). Swedish and US registry/cohort-based studies focused on SPLCs only and showed that the relative risk for these exceeded that for IPLC (8, 15, 16). Etiology of SPLCs may be shared by IPLC, including smoking, other environmental factors and hereditary predisposition but also field cancerization and treatment-related factors have been proposed as possible mechanisms for SPLC (5, 6). Risk of SPLC has been reported to be equal between smokers and never smokers which could imply involvement of hereditary or other unknown factors (16). Two US studies reported on the variables that influenced the probability of SPLC, including age at diagnosis of IPLC (maximal at 60-64 years), histology (highest for adenocarcinoma) and stage (highest for local) (15, 17). When the risk factors were combined and divided into decile the incidence difference between the extremes were over 4-fold (17). However, the risk stratification was heavily influenced by age of IPLC diagnosis (low risk for diagnosis below 45 and over 75 years, and advanced stages, particularly distant disease) (17).

We use data from the most recent update of the Swedish cancer registry (1961-2021) with focus on a cohort of patients diagnosed with IPLC during 1993-2021. As background information about Swedish IPLC, squamous cell carcinoma (SCC) was the main histological type of male LC when it reached a maximal incidence in 1982, while for women adenocarcinoma was always the main histological type and the incidence peaked as late as in 2018 (18, 19). Here we estimate risk of SPLC as cumulative proportion of patients developing SPLC by age, sex, histology and follow-up time. The data will guide thorax clinics to plan their follow-up schemes for SPLC in patients successfully treated for IPLC. The need to institute follow-up schemes for LC patients at risk of SPLC is linked to a more public heath related ambition of screening healthy at-risk individuals using low-dose computed tomography (CT) for which screening schemes are rolling-out or planned in many countries (20). The consequence will be increasing proportion of early-stage LC patients who need to be evaluated for risk of SPLC.

Methods

Data on LC occurrence were obtained from the Swedish cancer registry. LC was defined through ICD-7 code 1621, 'LC specified as primary'. For any reported cancer, the cancer registry makes an effort to include only primary cancers and we thus presume that multiple LCs are independent primaries (8). Nevertheless, in order to exclude mix-up of notifications we include only LCs diagnosed at least 1 month apart of each other. We additionally used the MM criteria for classifying LC cases as SPLC (see Introduction); however, only 8 potential SPLCs were deleted because of these criteria, indicating careful definition of SPLC by the cancer registry (**Supplementary Table 1**). The analyses considered patients born in Sweden, ensuring reliable tracking of patient cancer history.

In the Swedish cancer registry 98% of cancers are histologically verified. Data content and quality of the cancer registry has been thoroughly reviewed (9). Data on the main histological types were available through the whole study period and include adenocarcinoma code 96, SCC (146), small cell carcinoma 186, large cell carcinoma 196 and bronchoalveolar cancer (BAC) 76. As BAC is considered part of adenocarcinoma, we combined it with the "adenocarcinoma" category. The IPLC and SPLC definitions were restricted to the main four histologies. Data on tumor topography were available since 1993. Staging data (TNM, 6^{th} edition to 2009 and then 7^{th} edition) were almost complete after 2005 but mostly missing before 2004, and were not included in SPLC defining

criteria. We use only T stage data in analysis. For N, of a total of 443 patients, only 94 were other than N0; similarly for a total of 444 patients with M stage, only 35 were other than M0.

Statistical analysis

We analyzed data in competing risk setting, where competing events included death, SPLC diagnosis and diagnosis of any LC not meeting criteria for SPLC. This was modified for SPLC-histology analysis, where cancers with different histologies represented competing risks, representing mutually exclusive events. The follow-up started one month after IPLC diagnosis and was terminated at time of death, emigration, LC diagnosis or end of study (29th December 2021), whichever came earliest. The cumulative probability (cumulative incidence function) of competing events was estimated by nonparametric Aaalen-Johansen estimator, using cmprsk package in R (21).

Incidence rates were calculated as numbers of cases/100 000 person-years at risk by calendar period. Standardized incidence ratios (SIRs) for SPLC were estimated for patients diagnosed with IPLC in 1993-2021, as number of observed SPLC cases divided by expected number of cases based on IPLC incidence in background population. The start and termination of follow-up were the same as in the cumulative probability analyses. The estimates were standardized by sex, age (5-year groups), calendar year (10-year periods), education (proxy for socioeconomic status) and area of residence (large cities, southern and northern Sweden). The standardization should partially adjust for differences in smoking levels between LC patients; our earlier studies have shown over 2-fold differences in LC incidence between female and male educational and social groups (22, 23). We have recently published data on familial risk which could be identified for 15% of LC patients in 1961-2021 (24). However, as the focus in the present paper is for period 1993-2021, the proportion would be much smaller.

The 95% confidence intervals (CIs) for crude and standardized incidence rates were calculated by assuming that observed number of SPLC cases follows Poisson distribution. To control for potential non-Poissonian distribution of SPLC events, we have additionaly estimated bootstrap 95%-CI, where patients with IPLC were 1000-times sampled randomly with replacement to obtain 2.5^{th} and 97.5^{th} quantile of bootstrapped SIR distribution. We further report bootsrap-derived p-values for testing the hypothesis that younger age groups are associated with with higher marginal relative risk, calculated as $p=(|SIR_{Yboot}-SIR_{Oboot}\leq 0|+1)/(B+1)$, where $|SIR_{Yboot}-SIR_{Oboot}\leq 0|$ is number of non-positive samples in bootstrap distribution of differences between SIR values for younger and older age-group, respectively, and B=1000 is number of random samples. Bootstrapping was performed for patient subgroups in which age-groups had sufficient case numbers to ensure stable estimates (**Supplementary Table 4**).

All statistical analyses and data visualization were done using SAS (version 9.4) and R (version 4.4.0).

Results

Case numbers of IPLC and SPLC are shown for two calendar periods, 1993-2021 with most complete data (N for IPLC = 67,000), and 1961-2021 with larger overall case number (N=105,000) (**Supplementary Table 2**). In 1993-2021, case numbers for IPLCs were almost equal for women and men, but for SPLC women clearly outnumbered men (59.5 vs. 40.5%). Most SPLCs developed in

patients initially diagnosed with adenocarcinoma (56.9%) and in patients who were 60-69 old at IPLC diagnosis (43.8%).

The incidence of SPLC after histology-specific IPLC is shown in **Fig. 1** for period 1971-80 to 2011-21. On top, female and male rates increased sharply but did not differ; the increase in incidence was more than 3-fold in 30 years. No difference was noted between the incidence rates for SPLC after the four histological types of IPLC (CIs are given in the legend).

Stage distributions of IPLC and SPLC are shown by T classification according to histology in **Supplementary Table 3**. SPLCs diagnosed after adenocarcinoma were largely also adenocarcinomas, 81% for women and 71% for men. Adenocarcinoma as SPLC accounted for 63.9%, SCC for 19.4%, small cell for 9.6% and large cell for 9.1% of the four main histological types of SPLC. Adenocarcinomas dominated also after IPLC adenocarcinoma of T1 stage, accounting for 72% of all female and 66% of male second adenocarcinomas. For the other SPLC histologies the stage distribution of the corresponding IPLC was more variable and even T4 IPLC contributed of over 10% of SPLCs. IPLC of SCC histology was followed by an equal number of SPLCs of adenocarcinoma and SCC histology in women, whereas in men second SCC dominated (SCC-adenocarcinoma 27%, SCC-SCC 44%). SPLCs after small cell carcinoma where adenocarcinomas (40%, 38% in women, 50% in men) and SCCs (55%). SPLC after large cell carcinoma were mainly adenocarcinomas (51%), whereas SCCs accounted for 15%. Even though concordant adenocarcinoma was common in IPLC-SPLC sequence, discordant histology (112 vs. 37) was 3 times more common than concordant histology when IPLC was not adenocarcinoma.

Incidence rates for male and female IPLC and estimated smoking prevalence, as cited by Lee et al., are shown in **Supplementary Fig. 1A** (25). Male smoking prevalence started to decline already after 1950 and it reached 15% in 2005. LC incidence peaked at 30/100,000 in 1982 and declined to 16/100,000 in 2021. Female smoking prevalence increased sharply towards the early 1970s reaching the male prevalence at around 1990. Female incidence increased almost linearly until 2010, exceeding shortly thereafter male incidence. In **Supplementary Fig. 1B** only adenocarcinoma incidence is shown. Male rate increased relatively evenly to 9/100,000 in 2010 with a broad maximum. Female incidence shot up at year 2000 towards a sharp maximum at 12/100,000 in 2016.

The cumulative proportion (CumP) for competing events after any IPLC was dominated by deaths (**Supplementary Fig. 2**). Men died in larger proportions than women (**A** and **D**); CumPs were 0.762 vs. 0.678 in 2 years and 0.927 vs. 0.877 in 10 years. In 336 months (28 years) female SPLC reached CumP of 0.021 (**B**) while the share of LC not meeting the criteria for SPLC was marginal (**B**); in panel **C**, CumP of 0.0013 was reached in 12 months. CumP for SPLC in men reached 0.013 in 336 months (**E**) and 0.0009 in 12 months (**F**).

CumP in age-groups of any IPLC diagnosis is shown in **Supplementary Fig. 3**. By 10 years of follow-up those diagnosed at age before 50 years reached a CumP of 0.007 (**A**), while those diagnosed at age 50-69 years reached CumP of 0.013 (**B**) and those diagnosed at a higher age reached CumP of 0.008 (**C**). The 10-year CumP for female SPLC increased from 0.009 to 0.016 (1.8-fold) between periods 1993-2004 and 2005-2021 (**D, E**). The increase in male CumP was larger, from 0.004 to 0.01 (2.5-fold) (**F, G**).

CumP of sex-and histology-specific SPLC since IPLC diagnosis is shown in **Fig. 2**. There was a large sex difference for adenocarcinoma, female CumP reaching close to 0.014 (over a maximum follow-up time of up to 28 years) while the male CumP converged to a maximum below 0.006. The

CumP curves for SCC (0.004) and large cell carcinoma (0.0025) showed no sex-difference but the maximum for small cell carcinoma was higher for women (0.0021) than for men (0.0012).

CumP for sex-specific SPLCs after histology-specific IPLC is shown in **Fig. 3**. Female CumP of SPLC in 10 years after first adenocarcinoma was 0.019, after SCC it was 0.015, after small cell carcinoma it was 0.008 and after large cell carcinoma it was also 0.008. The respective CumPs for men were 0.013, 0.012, 0.002 and 0.005.

Relative risk (SIR) for a SPLC diagnosis, depending on histology of IPLC and age, is shown in **Table 1**. For all IPLC patients, and for those with adenocarcinoma and large cell carcinoma, the highest relative risk for having a SPLC was observed for patients below 60 years of age, while for SCC it was between ages 60 to 74 and for small cell carcinoma it was at age 75+ years. At age below 60 years female risk after adenocarcinoma risk was 9.95 (male 6.77). Female risk after SCC before age 60 years was also substantial, 6.23.

We further assessed relative risks for SPLC conferred after various T stages at IPLC diagnosis among women (**Table 2**). After any IPLC relative risks were highest before age 60 years but case numbers were few compared to age group 60 to 74 years for which SIRs declined from 5.91 for T1 to 1.29 for T4. Female SIRs after T1 IPLC adenocarcinoma was 13.62 (N=8) and 21.09 after T3 (N=3). The largest case numbers were for T1 at age group 60 to 74 years (N=83, SIR 5.99) and at age 75+ years (N=44, SIR 4.43).

Discussion

Using Swedish nation-wide cancer data we could identify 853 SPLCs from four histological types of IPLC that passed the MM criteria for SPLC (6). The incidence in SPLCs increased more than 3-fold in 30 years (**Fig.1**). The overall relative risk of SPLC diagnosis was 3.59, higher for women (4.16) than for men (2.99) and approximately equally high after adenocarcinoma and SCC. Case numbers of SPLCs diagnosed before age 60 were only 5% of all, but the relative risk was high, 6.68. The risk conferred after female adenocarcinoma in this age group was 9.95 (males 6.77). Risks were exquisitely high, 13.62 and 21.09 after rare female adenocarcinomas of stages T1 and T3 at age before 60 years. The current relative risk of SPLC of 3.59 is relatively high compared to other common cancers such as colon, breast, kidney and bladder cancers, for which the relative risks of second (concordant) primary cancers typically vary between 2.0 and 3.0 (10, 26). However, higher risks have been reported for skin cancers and virally predisposed cancers (26, 27).

When we followed incidence of SPLC from years 1971-80 onwards we observed an identical increase among women and men and after the four main histological types of IPLC. Data from the US Surveillance, Epidemiology and End Results (SEER) database showed similar results with larger case numbers from years 1992 to 2007 (15). In the present study the histological distribution of SPLC in 1993-2021 was adenocarcinoma 63.9%, SCC for 19.4%, small cell for 9.6% and large cell for 9.1%, which deviated only with a few % units from the US distribution for which data on large cell carcinoma were lacking (15).

In pair-wise analysis, the present data showed that SPLCs diagnosed after adenocarcinoma were largely also adenocarcinomas and more than half of these originated from IPLC cases of T1 stage without much sex difference. T1 prominence was not true for the other SPLC histologist and over 10% of any histological types of SPLC were diagnosed in T4 patients. IPLC of SCC histology was followed by an equal number of SPLCs of adenocarcinoma and SCC histology in women but in men second SCC dominated (SCC-adenocarcinoma 27%, SCC-SCC 43%). SPLCs after small cell

carcinoma where adenocarcinomas (40%) and SCCs (55%). After large cell carcinoma they were mainly adenocarcinomas (51%) and diverse other histologies. Thus, when IPLC presented with non-adenocarcinoma histology, 3 times more SPLCs were of discordant histology from IPLC which is another piece of evidence for the cases being independent SPLCs; recurrences from the IPLC should be dominated by the same histology.

The probability of SPLCs was dominated by female adenocarcinoma (CumP 0.014) while the male maximum remained close to 0.006 and female and male SCC reached 0.004 (**Fig. 2**). Five-year relative survival in LC has also doubled in this period in Sweden, however somewhat more for women than for men (28). In order to understand the CumP curves for histology-specific SPLCs we need to consider also the background incidence in IPLC. We checked the web site of the Swedish cancer registry that the incidence difference in period 2005-2021 was quite large in favor of adenocarcinoma vs SCC (approximate world standardized rates/100,000 were for women 9.8 vs 2.4 and for men 7.7 vs 4.3) (https://sdb.socialstyrelsen.se/if_can/val.aspx). Five-year relative survival for female adenocarcinoma in Sweden has been clearly better than that for SCC; for 2012 the difference was about 27 vs 20% (29). For male survival there was no difference, both about 17% (29). For small cell carcinoma survival was clearly lower, 8% for women and 5% for men. Thus, the large excess of female SPLC adenocarcinoma (**Fig. 2**) is likely to be the sum result of high incidence and survival of IPLC adenocarcinoma and high proportion of female SPLC adenocarcinoma (81%, male 71%) after first adenocarcinoma (**Supplementary Table 2)**. For men the difference in CumP between adenocarcinoma and SCC was smaller as the IPLC incidence in these cancers differed far less than that for women and survival was equal (see above). Female survival exceeds male survival not only in LC but in many other cancers which may imply that some sex-related biological or social factors, including alertness about early signs of cancer, play a role (19, 30).

The limitations of the present study include low case numbers, particularly after the rarer histological types of IPLC and in men. As a national study spanning a long calendar period we are lacking individual smoking data as well as treatment details for IPLC. During the current period the incidence of LC has changed extensively as shown in **Supplementary Fig. 1** and elsewhere (28, 31). The rapid increase among female smokers in the late 1960s appeared to boost the steep increase in adenocarcinoma 30 years later, which contributed to the epochal crossing of female and male LC incidence rates (18). In spite of the declining male smoking prevalence since 1960 and female prevalence since 1990 among LCs diagnosed in Sweden in 2023 only 16% of women and 11% of men were non-smokers (https://cancercentrum.se/globalassets/cancerdiagnoser/lunga-och-lungsack/kvalitetsregister/rapport/20241105_nlcr_nationell_rapport2023.pdf). Even though the identity of SPLC is likely to be correct, as the cases passed the MM criteria, the results are not informative of the detailed etiology of SPLCs.

In conclusion, we could describe a vastly increasing incidence in SPLCs in Sweden which was dominated by female adenocarcinoma reaching CumP of 0.014 compared to male adenocarcinoma of 0.006. CumP of SPLC increased past 10 years of IPLC diagnosis. Relative risk for any SPLC was 3.59 and it was highest of 9.95 after female adenocarcinoma diagnosed before age 60 years. Several LC computed tomography (CT)-based screening studies and some randomized trials have shown incidence and mortality reduction among high-risk populations as reviewed (5, 6, 20, 32). The application and funding of CT screening to population screening of risk groups are being discussed and some European professional organizations have collected a comprehensive background data bank on the theme **ERS / ESR factsheet**. These are beyond our scope but we believe that the present study may help to define potential target populations for such studies when launched (32-34).

Although we lack individual smoking data, the overwhelming proportion of Swedish LC patients have a smoking history. Based on the relative risks of SPLC the target population could be adenocarcinoma patients diagnosed before age 60 years.

ADDITIONAL INFORMATION

DATA AVAILABILITY

Anyone wishing to use these data should contact the National Board of Health and Welfare, Stockholm.

ETHICS

The study was approved by the Regional Ethical Review Board in Lund University, February 6, 2013 (Reference 2012/795 and subsequent amendments). Informed consent is not needed by law for use of national register data. The study was conducted in accordance with Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Design: KH
Acquisition of data: KS, JS.
Statistical analysis and interpretation: FZ, KH, AF, AH, RK
Manuscript writing: KH and all other authors.
Approval of the final text: All authors

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LEGENDS TO FIGURES

Fig. 1. The incidence of SPLC after histology-specific IPLC from period 1971-80 to 2011-21. On top (**A**), male and female rates (2011-2021 incidence [95% CI]: females 641.3 [571.4-717.5], males 596.6 [515.6-686.8]). Incidence rates for SPLC after the four histological types of IPLC (**B**, 2011-2021: adenocarcinoma 593.3 [528.2-664.1], SCC 690.3 [568.4-830.6], small cell carcinoma 578.7 [381.4-842.0], large cell carcinoma 700.5 [531.9-905.6]).

Fig. 2. Cumulative probability of histology-specific SPLC since start of follow-up in period 1993-2021. The shading shows 95% confidence intervals.

Fig. 3. Cumulative probability of histology-specific SPLC since start of follow-up in period 2005 to 2021 in females (upper row) and males (lower row). The shading shows 95% confidence intervals. The broken line marks the probability at 120 months (10 years).

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Table 1 SIR of SPLC for patients diagnosed with IPLC during 1993-2021. Reference rate correspond to IPLC incidence in background population.

			Age group					
		All ages		<60		60-74		75+
Histology IPLC	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI
All LC	662	3.59 [3.32-3.87]	37	6.68 [4.71-9.21]	375	3.88 [3.50-4.29]	250	3.04 [2.68-3.44]
Adenocarcinoma	380	3.70 [3.34-4.10]	28	9.18 [6.10-13.27]	209	3.84 [3.34-4.40]	143	3.17 [2.67-3.73]
SCC	167	3.60 [3.07-4.18]	3	3.31 [0.68-9.66]	94	4.20 [3.39-5.14]	70	3.02 [2.36-3.82]
Small cell	40	3.05 [2.18-4.15]	2	2.89 [0.35-10.43]	21	2.67 [1.65-4.09]	17	3.72 [2.17-5.95]
Large cell	75	3.36 [2.64-4.21]	4	4.51 [1.23-11.54]	51	4.23 [3.15-5.56]	20	2.13 [1.30-3.30]

Females

			Age group					
		All ages		<60		60-74		75+
Histology IPLC	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI
All LC	394	4.16 [3.76-4.59]	30	7.72 [5.21-11.02]	236	4.32 [3.79-4.91]	128	3.53 [2.95-4.20]
Adenocarcinoma	245	4.05 [3.56-4.59]	23	9.95 [6.31-14.94]	148	4.26 [3.60-5.00]	74	3.16 [2.48-3.97]
SCC	80	4.85 [3.84-6.03]	3	6.23 [1.28-18.20]	44	5.00 [3.63-6.71]	33	4.57 [3.15-6.42]

Males

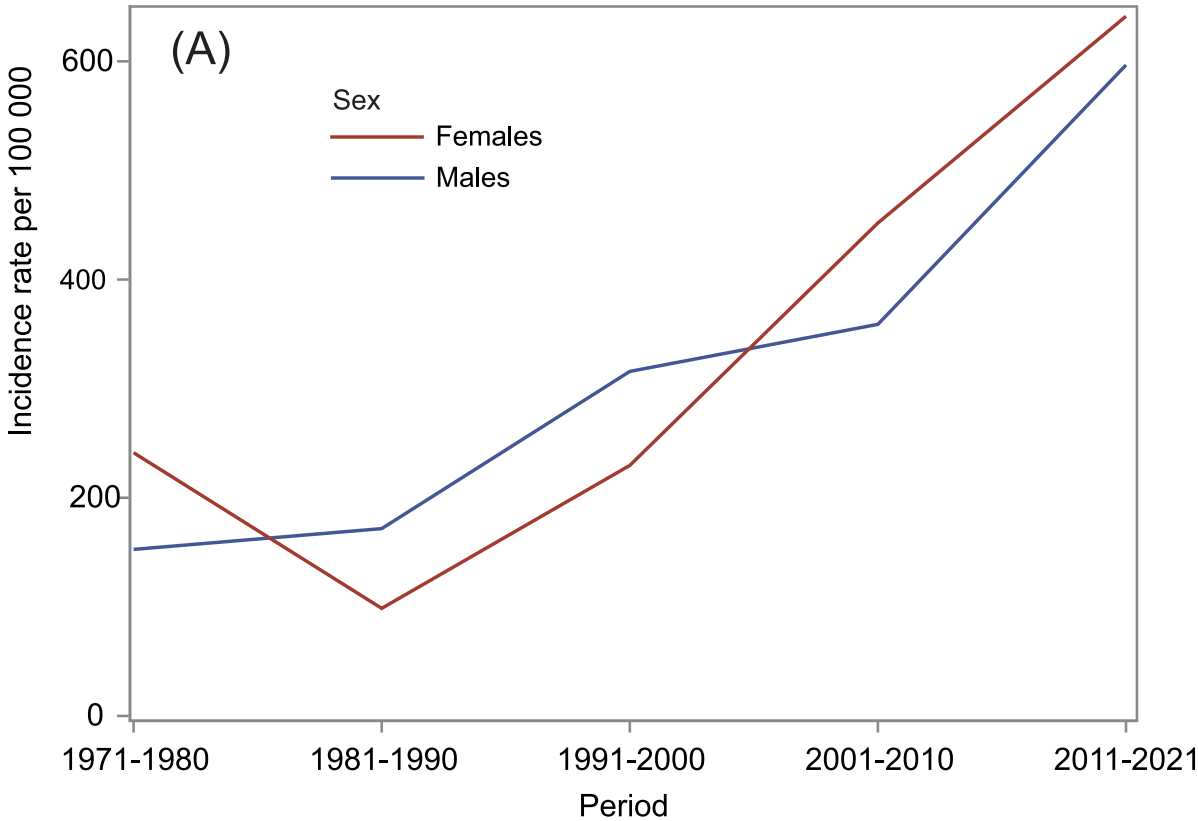
			Age group					
		All ages		<60		60-74		75+
Histology IPLC	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI
All LC	268	2.99 [2.64-3.37]	7	4.24 [1.71-8.74]	139	3.30 [2.78-3.90]	122	2.65 [2.20-3.17]
Adenocarcinoma	135	3.21 [2.69-3.80]	5	6.77 [2.20-15.81]	61	3.06 [2.38-3.99]	69	3.18 [2.47-4.02]
SCC	87	2.91 [2.33-3.59]	.		50	3.68 [2.73-4.85]	37	2.32 [1.64-3.20]

Table 2 SIR for SPLC in female patients diagnosed with IPLC by age and T stage of IPLC. Subset of 1993-2021 cohort with available staging data.

Females - all LC	T stage of IPLC							
	T1			T2			T3			T4		
Age group	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI
<60	8	10.98	[4.74-21.63]	5	6.30	[2.04-14.69]	3	12.53	[2.58-36.62]	2	3.7	[0.45-13.38]
60-74	106	5.91	[4.84-7.15]	49	3.76	[2.78-4.97]	10	2.30	[1.10-4.23]	11	1.29	[0.64-2.31]
75+	63	4.70	[3.61-6.02]	27	3.11	[2.05-4.52]	5	1.81	[0.59-4.23]	8	1.71	[0.74-3.37]

Females - adenocarcinoma	T stage of IPLC							
	T1			T2			T3			T4		
Age group	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI
<60	8	13.62	[5.88-26.84]	2	3.87	[0.47-13.96]	3	21.09	[4.35-61.63]	2	7.59	[0.92-27.41]
60-74	83	5.99	[4.77-7.42]	26	3.16	[2.07-4.64]	5	2.00	[0.65-4.67]	1	0.23	[0.01-1.3]
75+	44	4.43	[3.22-5.95]	13	2.36	[1.26-4.03]	2	1.29	[0.16-4.67]	1	0.4	[0.01-2.24]

Fig. 1


(A)
Sex
Females
Males
Incidence rate per 100 000
600
400
200
0
1971-1980
1981-1990
1991-2000
2001-2010
2011-2021
Period

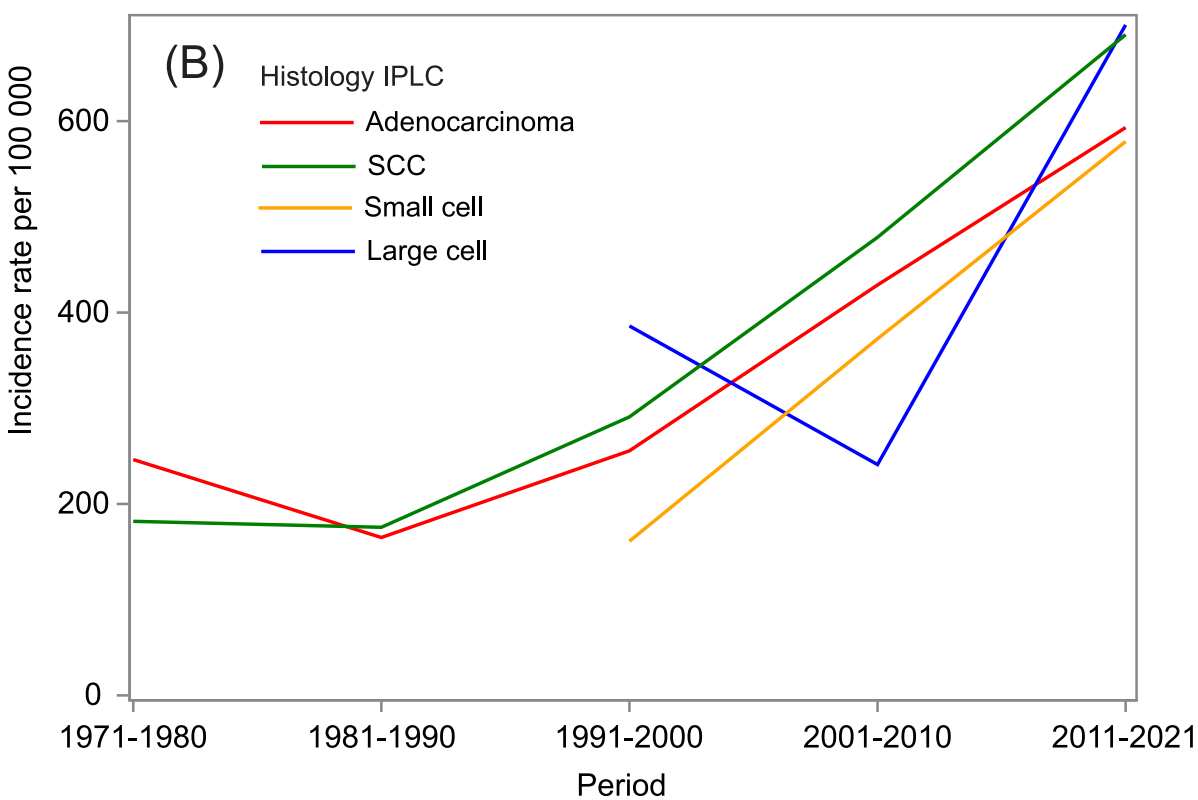
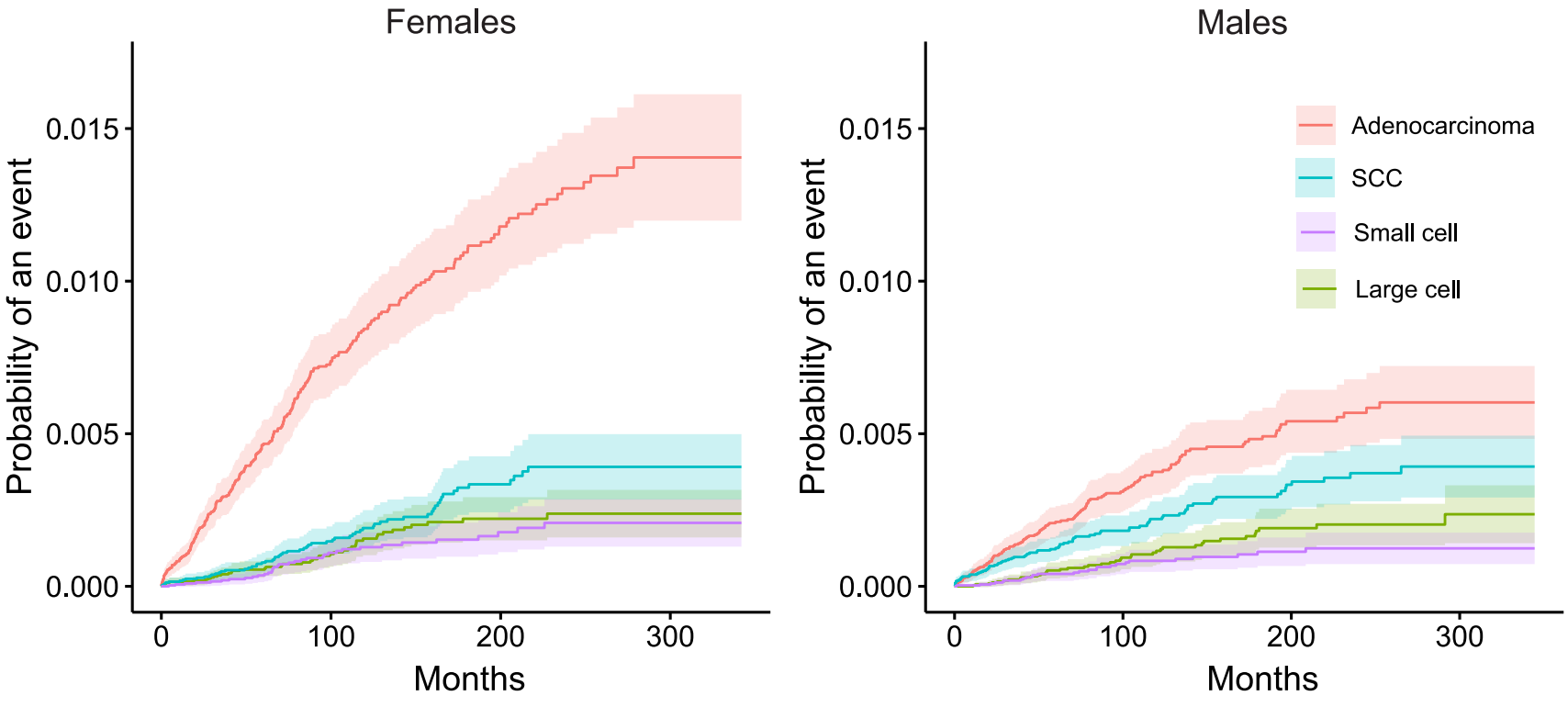

(B)
Histology IPLC
Adenocarcinoma
SCC
Small cell
Large cell
Incidence rate per 100 000
600
400
200
0
1971-1980
1981-1990
1991-2000
2001-2010
2011-2021
Period

Fig. 2


Females
Males
Probability of an event
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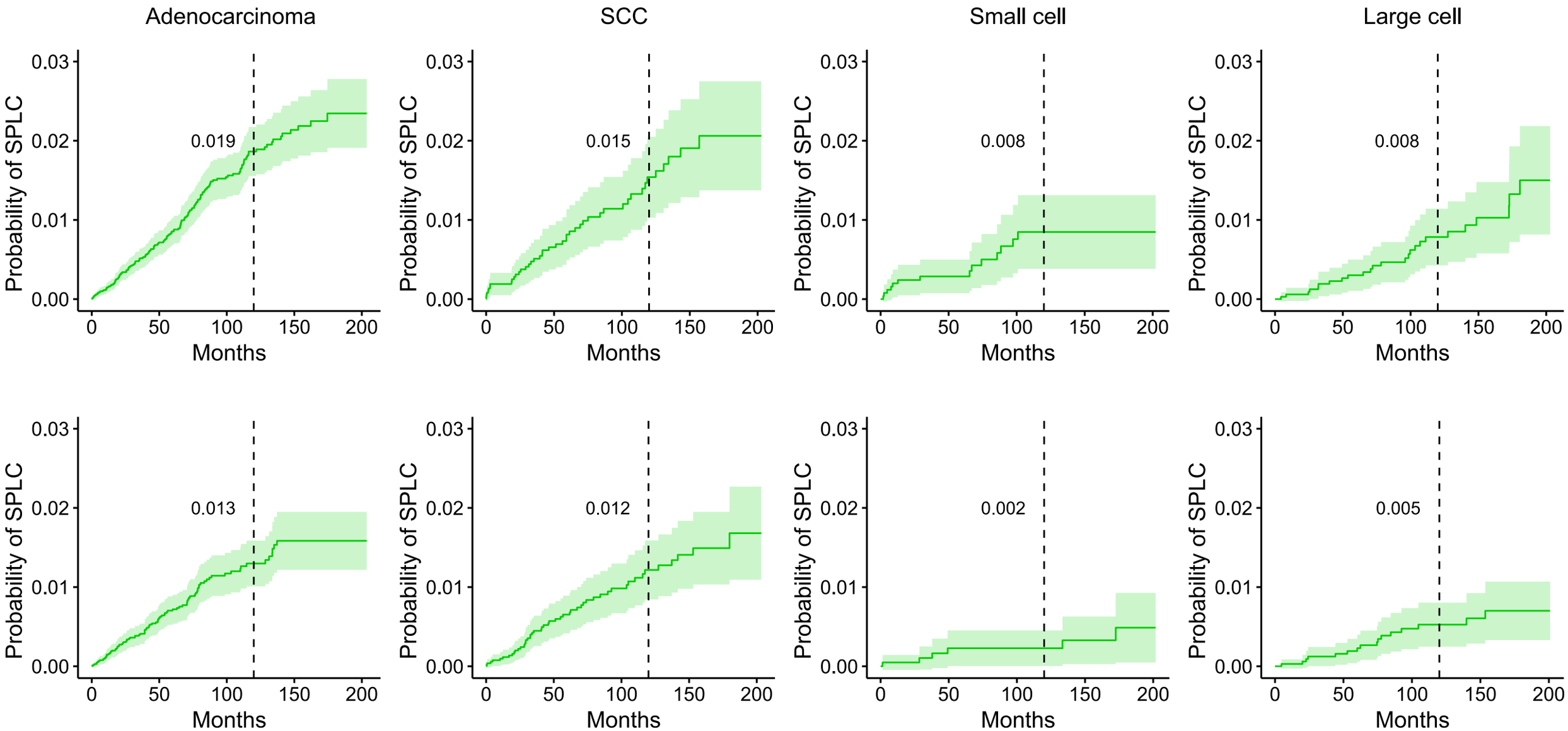
0.010
0.005
0.000
0
100
200
300
Months
Adenocarcinoma
SCC
Small cell
Large cell

Fig. 3


Adenocarcinoma
SCC
Small cell
Large cell
Probability of SPLC
Months
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0.015
0.008
0.008
0.013
0.012
0.002
0.005
0.00
0.01
0.02
0.03
0
50
100
150
200

Suppl. Table 1. Case numbers of SPLC by fulfilling individual adapted Martini Melamed criteria (cohort 1993-2021).

IPLC histology	MM 1	MM 1 or 2	MM 1 or 2 or 3
Adenocarcinoma	100	311	380
SCC	104	157	167
Small cell	38	40	40
Large cell	60	75	75
Total	**302**	**583**	**662**

MM 1: different histology
MM 2: > 2 years apart
MM 3: different lobe of lung

Suppl. Table 2. Case numbers of IPLC and SPLC by patient characteristics (cohort 1993-2021, modified MM criteria; cohort 1961-2021, all ICD7 1621 >= 1 month after IPLC)). IPLC included if a patient was at risk in the begining of follow-up.

	1993-2021		1961-2021	
	All IPLC	Developed SPLC	All IPLC	Developed SPLC
	Cases N (%)		Cases N (%)	
Sex				
Females	33344 (49.3 %)	394 (59. 5 %)	43054 (40.6 %)	462 (54.2 %)
Males	34223 (50.7 %)	268 (40.5 %)	62984 (59.4 %)	391 (45.8 %)
Histology of IPLC				
Adenocarcinoma	32869 (48.6 %)	380 (57.4 %)	41409 (39.1 %)	451 (52.9 %)
SCC	15131 (22.4 %)	167 (25.2 %)	30471 (28.7 %)	248 (29.1 %)
Small cell carcinoma	8071 (11.9 %)	40 (6.0 %)	10212 (9.6 %)*	48 (5.6 %)*
Large cell	11496 (17.0 %)	75 (11.3 %)	23946 (22.6 %)**	106 (12.4 %)**
Age at IPLC diagnosis				
0-49	1933 (2.9 %)	22 (3.3 %)	4484 (4.2 %)	51 (6.0 %)
50-59	7972 (11.8 %)	127 (19.2 %)	14967 (14.1 %)	179 (21.0 %)
60-69	21213 (31.4 %)	290 (43.8 %)	35554 (33.5 %)	364 (42.7 %)
70-79	26790 (39.6 %)	206 (31.1 %)	38726 (36.5 %)	238 (27.9 %)
80+	9659 (14.3 %)	17 (2.6 %)	12307 (11.6 %)	21 (2.5 %)

*Histological subtype recognized since 1986. **Numbers shown for PAD label 196, which before 1986 coded for 'unspecified type'.

Suppl. Table 3. Case numbers of IPLC and subsequent SPLC by histology and T stage of IPLC (2005-2021). First column for each sex shows case numbers of IPLC that did not develop SPLC during follow-up period. IPLC included if a patient was at risk in the begining of follow-up.

		Females						Males					
			SPLC histology						SPLC histology				
		Non SPLC	Adeno-carcinoma	SCC	Small cell	Large cell	Total SPLC	Non SPLC	Adeno-carcinoma	SCC	Small cell	Large cell	Total SPLC
IPLC histology	IPLC T stage	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma	T1	688	8	.	.	.	8	444	1	.	.	3	4
	T1a	1268	36	1	.	.	37	802	20	1	1	.	21
	T1b	1646	45	1	.	2	48	1031	14	2	1	2	18
	T1c	478	7	1	.	.	8	357	5	2	.	1	8
	T2	938	1	.	.	.	1	750	1	.	.	.	1
	T2a	1866	14	5	.	.	19	1410	4	4	.	1	9
	T2b	754	3	2	2	1	8	620	4	.	.	1	5
	T3	1735	5	1	4	.	10	1410	3	3	1	.	6
	T3a	.	.	.	.	.	.	1	.	.	.	.	.
	T4	4195	16	2	4	1	23	3136	7	2	2	2	12
	Ta	.	.	.	.	.	.	1	.	.	.	.	.
	Tx	205	3	.	.	.	3	219	2	.	.	.	2
	Total	13773	134	13	10	4	165	10181	61	14	5	10	86
SCC	T1	128	1	.	.	.	1	152	1	1	.	.	2
	T1a	181	2	1	.	2	5	187	1	4	2	2	9
	T1b	219	2	3	1	2	8	258	4	5	3	.	12
	T1c	82	1	2	.	.	3	92	1	2	.	.	3
	T2	338	.	.	.	.	.	593	.	.	.	.	.
	T2a	402	4	2	1	1	8	550	1	3	1	.	5
	T2b	284	.	.	.	2	2	362	.	1	.	1	2
	T3	663	1	1	1	2	5	947	2	2	1	.	5
	T4	1242	1	2	1	4	8	1908	3	3	3	1	10
	T4a	1	.	.	.	.	.	.	.	.	.	.	.
	Tx	22	1	1	.	.	2	35	.	.	.	.	.
	Total	3562	13	12	4	13	42	5084	13	21	10	4	48
Small cell	T1	68	.	.	.	.	.	53	.	.	.	.	.
	T1a	70	.	1	.	.	1	55	.	.	.	.	.
	T1b	97	1	4	.	.	5	91	2	1	.	.	3
	T1c	40	1	1	.	.	2	28	.	.	.	.	.
	T2	145	.	.	.	.	.	161	.	.	.	.	.
	T2a	193	1	1	.	1	3	146	1	1	.	.	2
	T2b	89	1	.	.	.	1	69	.	.	.	.	.
	T3	302	1	.	.	.	1	285	.	.	.	.	.
	T4	1430	.	1	.	.	1	1055	.	1	.	.	1
	T4a	1	.	.	.	.	.	.	.	.	.	.	.
	Tx	46	.	.	.	.	.	56	.	.	.	.	.
	Total	2481	5	8	.	1	14	1999	3	3	.	.	6
Large cell	T1	145	.	.	.	.	.	141	.	1	.	.	1
	T1a	171	4	.	.	1	5	110	.	1	.	1	2
	T1b	182	3	1	1	1	6	179	.	.	.	.	.
	T1c	35	.	.	.	.	.	29	.	1	.	.	1
	T2	430	.	.	.	.	.	446	2	.	.	.	2
	T2a	303	.	.	2	.	2	298	1	.	1	1	3
	T2b	144	1	.	1	.	2	175	1	.	.	.	1
	T3	506	2	.	.	.	2	578	1	.	.	.	1
	T4	1291	4	1	3	.	8	1269	1	1	1	.	3
	Tx	49	.	.	.	.	.	50	.	.	.	.	.
	Total	3256	14	2	7	2	25	3275	6	4	2	2	14
Total		**23072**	**170**	**35**	**21**	**20**	**242**	**20539**	**83**	**42**	**17**	**16**	**154**

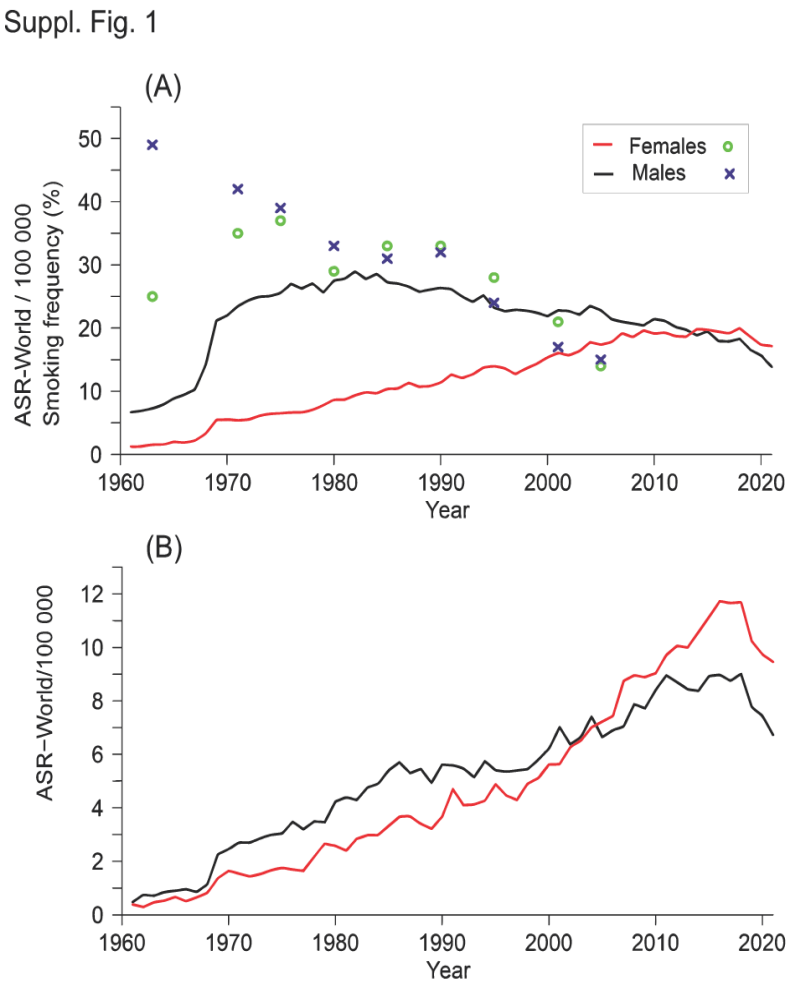
Suppl. Table 4. SIR estimates with bootstrap 95% confidence intervals for all patients and for females, all IPLC and adenocarcinoma only. The younger age tended to be associated with higher relative risk (bootstrap p-values for SIR difference: All LC : $SIR_{<60}$>SIR_{60-74} p=0.006, SIR_{60-74}>SIR_{75+} p=0.002, $SIR_{<60}$>SIR_{75+} p<0.001; Adenocarcinoma: $SIR_{<60}$>SIR_{60-74} p<0.001, SIR_{60-74}>SIR_{75+} p=0.038, $SIR_{<60}$>SIR_{75+} p<0.001; Females: $SIR_{<60}$>SIR_{60-74} p=0.006, SIR_{60-74}>SIR_{75+} p=0.038, $SIR_{<60}$>SIR_{75+} p<0.001; Adenocarcinoma: $SIR_{<60}$>SIR_{60-74} p=0.003, SIR_{60-74}>SIR_{75+} p=0.027, $SIR_{<60}$>SIR_{75+} p=0.002)

			Age group					
	All ages		<60		60-74		75+	
Histology IPLC	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI
All LC	662	3.59 [3.30-3.87]	37	6.68 [4.67-8.97]	375	3.88 [3.50-4.26]	250	3.04 [2.67-3.41]
Adenocarcinoma	380	3.70 [3.35-4.05]	28	9.18 [5.93-12.31]	209	3.84 [3.30-4.35]	143	3.17 [2.68-3.68]

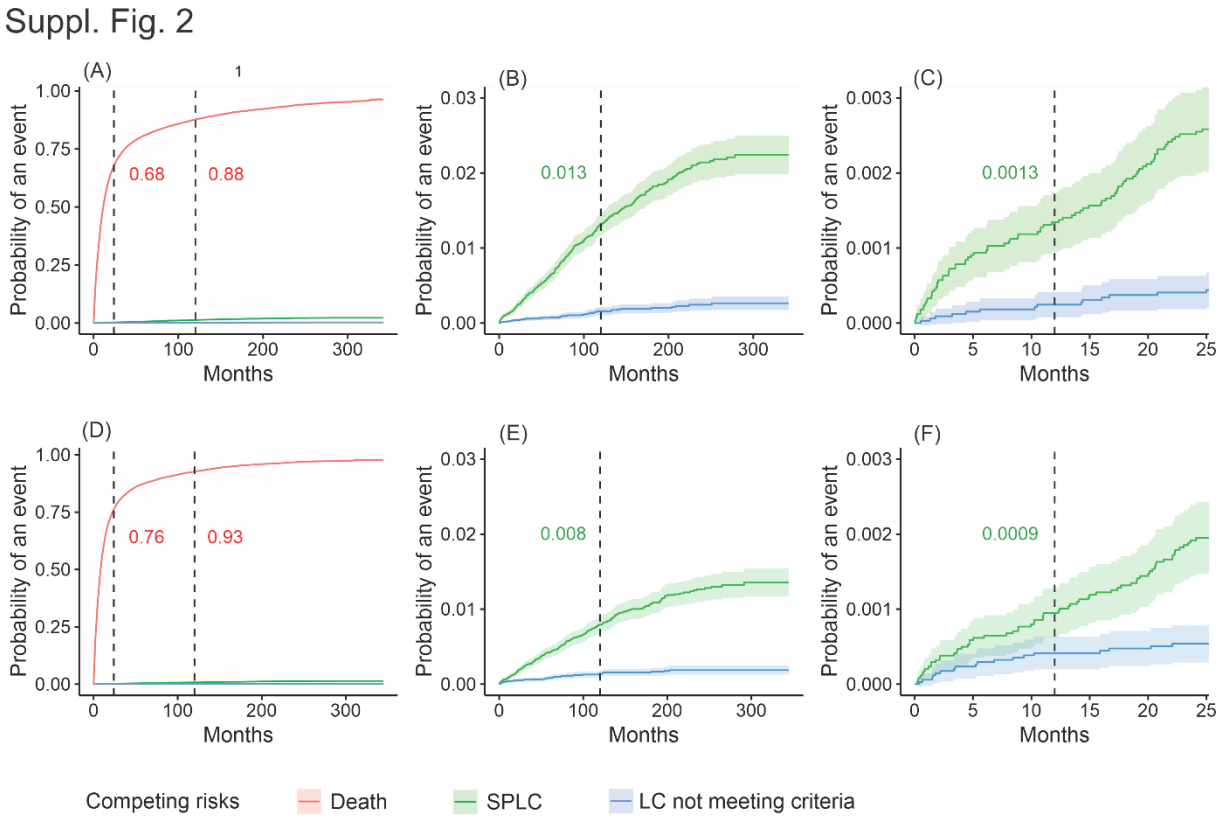
Females

			Age group					
	All ages		<60		60-74		75+	
Histology IPLC	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI	N	SIR 95%CI
All LC	394	4.16 [3.77-4.58]	30	7.72 [5.12-10.47]	236	4.32 [3.78-4.87]	128	3.53 [2.94-4.15]
Adenocarcinoma	245	4.05 [3.51-4.56]	23	9.95 [6.35-14.14]	148	4.26 [3.57-4.91]	74	3.16 [2.46-3.91]

Suppl. Figure 1 Solid lines: Age-standardized (World) male and female incidence of all lung cancers (**A**) and adenocarcinoma (**B**) for period 1961- 2021. Individual points show the estimated frequency of smokers in the population older than 20 years in Sweden (data collected from Lee et al. 2012).



Suppl. Figure 2 CumP of competing events in patients diagnosed with primary lung cancer (1993-2021) in females (**A**-**C**) and males (**D**-**F**)**.** The segmented lines mark 2 and 10 years of follow-up in (**A**), 10 years of follow-up in (**B**) and 1 year of follow-up in (**C**).



Suppl. Figure 3 CumP of SPLC by age of IPLC diagnosis (**A**-**C**,1993-2021) . **(D-G)** CumP of SPLC by period of IPLC diagnosis and sex.

Suppl. Fig. 3